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(71) Applicants
**Eliane Marie-Therese Lauzanne-Morelle**
**170 Avenue Parmentier**
**75010 Paris France**
**Jean Valentin Morelle**
**170 Avenue Parmentier**
**75010 Paris**
**France**

(72) Inventors
**Jean Valentin Morelle**
**Eliane Marie-Therese Lauzanne-Morelle**

(74) Agents
**Serjeants**
**25 The Crescent**
**King Street**
**Leicester LE1 6RX**

# (54) Compositions containing N-butyryl alpha-aminoacids

(57) In a composition for use in the cosmetic, hygienic, therapeutic or agricultural field, the active ingredient is an N-butyrylate of at least one alpha-amino acid or a salt of such an N-butyrylate with an inorganic, organic or biologic base or with a metal. The active ingredient may be the product of butyrylation of a mixture of amino acids obtained by the complete hydrolysis of a protein e.g. keratin, collagen or casein.

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SPECIFICATION

**Compositions c ntaining n-butyryl alpha-aminoacids**

*DESCRIPTION*

The invention relates to new compositions in which the active ingredient is an N-butyrylate of at least one alpha-aminoacid.

It is known to acylate aminoacids or mixtures of the same with fatty acids having more than five carbon atoms in the chain. These known acylates are liposoluble but generally insoluble in water and in usual solvents.

The applicants have disclosed that acylation of alpha-aminoacids or of mixtures of the same with butyric acid leads to new acylates which are simultaneously lipsoluble in water and in a large variety of polar and nonpolar solvents. Particularly, the N-butyrylation of amino acids or of mixtures of the same gives products soluble in alcohols, ketones, ethyl acetate, benzene, chloroform, diethyl ether and the like. Of course liposolubility, the hydrosolubility and the solubility in various solvents vary in relationship with the nature of the aminoacids. These butyrylates are also solube in mixtures of polar and nonpolar solvents such as methanol and chloroform but are insoluble in petroleum ether and in hexane. Some of them are insoluble in isopropyl ether. Compared with the lipoaminoacids obtained by acylation of aminoacids or of mixtures of the same by fatty acids having more than five carbon atoms in the chain, the acylation by butyric acid leads to compounds presenting a higher acidifying power of strictly biological origin (this is the acidity of the liberated carboxyl groups) due to the shorter length of the acylating chain.

The compounds of the invention present a better penetration for instance through the skin and also are efficient at lower doses than the previously known lipoaminoacids.

Accordingly the invention relates to compositions for use in various fields such as the cosmetic, hygienic, therapeutic and agricultural fields in which the active ingredient is an N-butyrylate of at least one alpha-aminoacid of a salt of such an N-butyrylate with an inorganic, organic or biologic base or with a metal.

According to the invention the alpha-aminoacid may be a mixture of the same obtained by any appropriate route and for instance the mixture of aminoacids obtained by the complete hydrolysis of a protein.

The result of the butyrylation of an aminoacid or of a mixture of aminoacids gives, in all cases, N-butyrylated derivatives; however, for those aminoacids that present other basic functions, these functions may also be partially or completely acylated by butyric acid.

As to the salts in these N-aylates of aminoacids or of mixtures of the same, it is to be understood the salts obtained by the action of any appropriate inorganic or organic bases (for instance triethanolamine, diethylamine, morpholine, and various basic aminoacids such as lysine, aginine and ornithine) or biologic bases such as choline and guanidine. The corresponding salts are obtained by mere reaction of the previously obtained N-butyrylates on the selected base. Metal salts of the N-butyrylates of the invention may be easily obtained by reacting the N-butyrylates on the hydroxide or carbonate of the selected metal in warm conditions; preferred metals are those known as oligo-elements.

To obtain the N-butyrylates used in the invention, the preferred route comprised the use of butyric anhydride which allows a complete reaction of the aminoacid with concommitent of free butyric acid; a stoichiometric excess of from 10% to 25% is preferred but when the aminoacid treated has other functions that might by acylated, it will be necessary to take into account all these functions in order to determine the appropriate proportions of butyric anhydride to use.

The following Examples illustrate the invention.

*Example 1 – N-Butyrylglycine*

30 g (0.4 mol) of glycine were poured into a 500 ml reactor fitted with stirring means and warmed by a water bath. 40 ml of 30% sodium hydroxide solution were then slowly added under stirring. When the reaction mixture cleared, 65 g of butryic anhydride were slowly added, while maintaining pH between 10 and 10.5 by the end of the addition (temperature 40–45°C). The reaction mixture was warmed at 70°C for half an hour and allowed to cool. To obtain the N-butyrylglycine from its sodium salt, hydrochloric acid was slowly added under stirring, until a pH of 2 was reached. This led to the appearance of an oily supernatant phase which was separated off and distilled under reduced pressure (oil-bath) to eliminate water and hydrochloric acid. After cooling, petroleum ether was added to precipitate N-butyrylglycine and eliminate butyric acid; this treatment was repeated twice.

Yield 51 g (88%) of a product, analysis of which showed good correspondence with theory (M.W. 151; $C_6H_{11}NO_3$). Acid index found : 382 (Theory: 386).

*Example 2 – N-Butyryl phenylalanine*

This preparation was conducted as described in Example 1, but using 33 g (0.2 mol) of phenylalainine in place of the glycine and 36 g of butyric anhydride.

Yield 42 g (90%) of a product, the analysis of which showed good correspondence with theory (M.W. 235; $C_{13}H_{17}NO_3$). Acid index found 235 (Theory: 238).

*Example 3 – N-Butyrylthreonine*

This preparation was conducted as described in Example 1, but using 36 g (0.3 mol) of theronine in place of the glycine and 51 g of butryic anhydride.

Yield 57 g (99%) of a product, analysis of which showed good correspondence with theory (M.W. 213; $C_8H_{15}NO_4$). Acid index found: 293 (Theory: 296).

*Example 4 – N-Butyrylaspartic acid*

This preparation was conducted as described in Example 1, but using 53 g (0.4 mol) of aspartic acid in place of the glycine and 64 g of butyric anhydride. After the elimination of water and hydrochloric acid, it was necessary to eliminate the remaining butyric acid by distillation under reduced pressure at 130–140°C (oil bath). The anhydrous residue was treated by an equal weight of distilled water, then by carbon black.

Yield 75 g (94%) of a product, analysis of which showed good correspondence with theory (M.W. 227; $C_8H_{13}NO_5$). Acid index found: 382 (theory 386).

*Example 5 – N-butyrylvaline*

This preparation was conducted as described in Example 1 but using 58 g (0.5 mol) of valine in place of the glycine and 85 g of butryic anhydride. As the N-butyrylvaline is poorly soluble in cold water, the elimination of butyric acid was made by washing with icy water.

Yield 85 g (92%) of a product, analysis of which showed good correspondence with theory (M.W 187; $C_9H_{17}NO_3$).
Acid index found: 294 (Theory: 297).

*Example 6 – N-Butyrylleucine*

This preparation was conducted as described in Example 5, but using 65 g of leucine (0.5 mol) in place of the valine.

Yield 89 g (92%) of a product, analysis of which showed good correspondence with theory (M.W. 201; $C_{10}H_{19}NO_3$). Acid index found: 277 (Theory: 280).

*Example 7 – N,N'-Dibutyryllysine*

This preparation was conducted as described in Example 1, but using 60 g of a 50% solution of lysine (0.2 mol) in place of the glycine and 64 g of butyric anhydride.

Yield 51 g (85%) of a product, analysis of which showed good correspondence with theory (M.W. 286; $C_{14}H_{26}N_2O_4$). Acid index found: 193 (Theory: 195).

*Example 8 – N-Butyrylproline*

This preparation was conducted as described in Example 1, but using 23 g (0.2 mol) of proline in place of the glycine and 40 g of butryic anhydride.

Yiele 34 g (92%) of a product, analysis of which showed good correspondence with theory (M.W. 185; $C_9H_{15}NO_3$). Acid index found: 304 (Theory: 302).

*Example 9 – N-butyryl- and N,N'-dibutyryl-hydroxyproline*

This preparation was conducted as described in Example 1, but using 52 g (0.4 mol) of hydroxyproline in place of the glycine and 75 g of butryic anhydride.

Yield 75 g (87%) of a product, analysis of which showed a mixture of 35% of the mono-derivative and 65% of the di-derivative for which theory is:
M.W. 201, $C_9H_{15}NO_4$, acid index for mono-
M.W. 271, $C_{13}H_{21}NO_5$, acid index 207 for di-
Found value for acid index is 230.

*Example 10 – N,N'-Dibutyrylhydroxylysine*

This preparation was conducted as described in Example 1, with 32 g (0.2 mol) of hydroxylsine in place of the glycine and 40 g of butryic anhydride.

Yield 53 g (88%) of a product, analysis of which showed good correspondence with theory (M.W. 302; $C_{14}H_{26}N_2O_5$). Acid index found: 187 (Theory: 184).

*Example 11 – N-Butyrylmethionine*

This preparation was conducted as described in Exampl 1, but using 45 g (0.3 mol) of methionine in place of the glycine and 50 g of butyric anhydride.

Yield 61 g (92%) of a product, analysis of which showed good correspondence with theory

(M.W. 219; $C_9H_{17}NO_3S$). Acid index found: 257 (Theory: 255).

*Example 12 – N,N'-Dibutyrylcystine*

This preparation was conducted as described in Example 1, but using 48 g (0.2 mol) of cystine in place of the glycine and 64 g of butyric anhydride.

Yield 73 (91% of a product, analysis of which showed good correspondence with theory (M.W. 380; $C_{14}H_{24}N_2O_6S_2$). Acid index found: 305 (Theory: 294).

*Example 13 – N-Butyrylcysteine*

This preparation was conducted as described in Example 1, but using 48 g (0.4 mol) of cysteine in place of the glycine and 64 g of butyric anhydride.

Yield 71 g (97%) of a product, analysis of which showed good correspondence with theory (M.W. 191; $C_7H_{13}NO_3S$). Acid index found: 307 (Theory: 297). SH found: 16.8 (Theory: 17.1).

The following Examples relate to the preparation of butyrylates of non-separated mixtures of aminoacids obtained by the complete hydrolysis of natural proteins. As these mixtures retain substantially the quantitative and qualitative proportion of aminoacids existing in the starting proteins, they are identified by a similar name.

The first step comprises the preparation of the protein hydrolysate from the selected protein. 200 g of the protein are treated conventionally by concentrated hydrochloric acid and the absence of peptides is checked by the Biuret test, after which the solution is neutralised (pH 6.5–7), treated with carbon black and filtered. The solution thus obtained is titrated against formaldehyde to determine the amine functions available for butyrylation and the amount of butyric anhydride to be used. With a sample of the hydrolysate a dry extract is prepared, weighted, treated with methanol to eliminate sodium chloride and once more titrated against formaldehyde.

This preliminary work allws the butyrylation to be conducted using the appropriate proportions of reactants.

*Example 14 – Butyrylcollagenic acid*

The starting protein was gelatin. The average molecular weight of aminoacids of the hydrolysate was 110. 200 ml of the titrated hydrolysate, containing about 50 g of aminoacids was treated as described in Example 1 with 80 g of butryic anhydride. The separation of the butyrylate was conducted by distillation as described in Example 4 above and led to 74 g (92%) of a product, analysis of which showed good correspondence with theory. Nitrogen titration found: 8.2 % (Theory: 8%)
Acid index found: 335 (Theory: 327).

*Example 15 – Butyrylkeratinic acid*

The starting protein was horn. The average molecular weight of the aminoacids of the hydrolysate was 120. The dosage of acylable amine functions is made with reference to cystine. The preparation is conducted as described in Example 14 from 300 ml of hydrolysate and 80 g of butryic anhydride; to obtain a better solubility of the acylates of valine, leucine and isoleucine, 3 to 5% of propyleneglycol was added.

Yield 87 g (96%) of a product, the analysis of which showed an acceptable correspondence with theory. Nitrogen titration found: 8.2% (Theory 7.4%); the difference comes from the presence of diabasic compounds in the mixture.

Acid index found: 287; for butyrylcystine, the theory is 294.

*Example 16 – Butyrylcasenic acid*

The starting protein was casein. The average molecular weight of the aminoacids of the hydrolysate was 120. The preparation is conducted as described in Example 14, from 300 ml of hydrolysate containing about 41 g of aminoacid and 60 g of butyric anhydride.

Yield 63 g (95%) of a product, analysis of which showed a good correspondence with theory. Nitrogen titration found: 8.2% (Theory 7.3%).

Acid index found: 260 (Theory 253).

The compositions according to the invention preferably comprise from 0.1 to 5% by weight of the active ingredient together with an appropriate carrier, the use of higher contents of active substances is generally not necessary. Examples of various compositions are given below:

A) *Cosmetic and hygienic field*

1) Creams for skin care

a) Butyrylhydroxy proline at 50% 3
steraine 5
Polyoxyethyoene cetyl alcohol 5
Isopropyl palmitate 10
Glycerol 10
Antiseptic and water to 100.

b) Butyrylproline 1
Carrier as in a) above.

c) Butyrylcystine 1
Carrier as in a) above

d) Butyrylhydroxyproline at 50% 2
Polyoxyethyleneglycol stearate 5
Antiseptic agent and water to 100.

e) Butyrylglycine 2
Carrier as in a) above.

f) Butyrylcollagenic acid 2
Carrier as in a) above.

g) Butyrylcaseinic acid 1
Butyrylkeratinic acid 1
Carrier as in a) above.

h) Aluminium butyryl collagenate 2
Carrier as in a) above

N.B. – This cream is active in the prevention of perspiration.

2) Lotions for hair care

a) Butyrylcysteine 1
Ethanol 15
Water to 100

b) Butyrylmethionine 1
Water to 100.

c) Butyrylcystine 0.5
Butyrylmethionine 0.5
Propyleneglycol 5
Water to 100.

N.B.– These lotions apply to animals.

Lotions for nail care

a) Butyrylcystine 1
Water to 100

b) Butyrylmethionine 1
Ethanol 15
Water to 100.

4) Tooth paste

Calcium butyrylcollagenate 3
Kaolin 17
Tricalcium phosphate 17
Glycerol 10
Sorbitol 10
Lauryl sulphate ether 2
Antiseptic, flavour and water to 100.

B) *Therapeutic field*

The compositions are substantially comparable to those for cosmetic or hygi nic use but comprise higher amounts of active ingredients.

a) Butyrylcollagenic acid at 50 % 5
Glycerol stearate 10
Glycerol 10
Perhydrosqualene 10
Antiseptic and water to 100.

b) Butylrylhydroxyproline at 50 % 6
Carrier as in a) above.

c) Zinc butyrylhydroxyprolinate 5
Carrier as in a) above.

d) Butyrylhydroxylysine 1
Butyrylhydroxyproline at 50 % 4
Carrier as in a) above.

e) Butyrylhydroxyproline at 50 % 5
Glycerol stearate 5
Glycerol 10
Isopropyl palmitate 10
Polyoxyethylenecetyl alcohol 5
Antiseptic and water to 100.

f) Butyrylhydroxyproline at 50 % 5
Glycerol 10
Water to 100.

N.B.– Compositions e) and f) present antalgic properties.

C) *Agricultural field*

1) Treatment of seeds and roots

a) Butyrylproline 2
Bentonite 98

b) Copper or zinc butyrylproline 2
Bentonite 98

c) Butyrylmethionine or butyrylcystine 0.1 to 1
Bentonite or kaolin to 100

d) Butyrylkeratinic acid at 50 % 4
Bentonite 96

e) Copper butyrylkeratinate 2
Water 98

f) Copper butyrylcollagenate 2
Kaolin 98

2) Treatment of leaves

a) Butyrylhydroxyproline at 50% 2
Water 98

b) Butyryl proline 0.1 to 2
Water 100

c) Copper butyrylprolinate 1
Water 99

d) Butyrylproline 0.05
Copper butyrylprolinate 0.05
Calcium butyrylprolinate 0.05
Water 100

e) Butyrylmethionine or butyrylcystine 0.05 to 0.5
Water 100

f) Copper butyrylcollagenate 2
Water 98

g) Zinc butyrylkeratinate 2
Water 98

CLAIMS

1. A composition for use in the cosmetic, hygienic, therapeutic or agricultural field, in which the active ingredient is an N-butyrylate of at least one alpha-amino acid of a salt of such an N-butyrylate with an inorganic, organic or biological base with a metal.

2. A composition according to claim 1 in which the active ingredient is the product of butyrylation of a mixture of aminoacids obtained by the complete hydrolysis of a protein.

3. A composition according to claim 1 or claim 2 containing from 0.1 to 5% of the active ingredient.

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